THYROID
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Are Detection and Treatment of Thyroid Insufficiency in Pregnancy Feasible?

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A workshop entitled, "The Impact of Maternal Thyroid Diseases on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening," was held in Atlanta, Georgia, January 12–13, 2004. The workshop was sponsored jointly by The National Center on Birth Defects and Developmental Disabilities of The Centers for Disease Control and Prevention (CDC) and The American Thyroid Association. This paper reports on the individual session that examined the ability to detect and treat thyroid dysfunction during pregnancy. For this session, presented papers included: "Laboratory Reference Values in Pregnancy" and "Criteria for Diagnosis and Treatment of Hypothyroidism in Pregnancy." These presentations were formally discussed by invited respondents and by others in attendance. Salient points from this session about which there was agreement include the following: thyrotropin (TSH) can be used as marker for hypothyroidism in pregnancy, except when there is iodine deficiency usually evidenced by elevated serum thyroglobulin (Tg). We need more longitudinal studies of TSH during pregnancy in iodine-sufficient populations without evidence of autoimmune thyroid disease to develop trimester-specific TSH reference ranges. Current free thyroxine (FT_4) estimate methods are sensitive to abnormal binding-protein states such as pregnancy. There is no absolute FT_4 value that will define hypothyroxinemia across methods. Total thyroxine (TT_4) changes in pregnancy are predictable and not method-specific. TT_4 below 100 nmol/L (7.8 μg/dL) is a reasonable indicator of hypothyroxinemia in pregnancy. Women with known hypothyroidism and receiving levothyroxine (LT_4) before pregnancy should plan to increase their dosage by 30% to 60% early in pregnancy. Women with autoimmune thyroid disease prior to pregnancy are at increased risk for thyroid insufficiency during pregnancy and postpartum thyroiditis and should be monitored with TSH during pregnancy.

Introduction

THIS REPORT contains the summaries of several papers presented at a workshop held in Atlanta, Georgia, January 12–13, 2004, to address "The Impact of Maternal Thyroid Diseases on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening." The purpose of this session was to examine the ability to detect and treat thyroid dysfunction. This session was organized and moderated by Dr. Susan Mandel.

"Laboratory Reference Values in Pregnancy" —Dr. Carole A. Spencer

The complex hormonal changes affecting free thyroxine (FT_4) availability to mother and fetus have been described earlier at this workshop by Dr. Daniel Glinoer (1). In view of the coordinated trimester-specific changes in thyrotropin (TSH) and FT_4 occurring during pregnancy and the vulnerability of the fetus during the first trimester before the fetal thyroid becomes active, trimester-specific TSH and FT_4 reference ranges are needed for evaluating pregnant patients (Fig. 1). Nonpregnant reference ranges may be misleading during the rapidly changing hormonal environment of pregnancy. During pregnancy, TSH is a more sensitive marker of thyroid status than FT_4, just as it is in nonpregnant patients, and it reflects the physiologic log/linear relationship of TSH to FT_4. Reference ranges for TSH and other thyroid tests are typically established from an appropriate cohort of subjects that have been rigorously selected as being euthyroid. Iodine insufficiency and autoimmune thyroid conditions (using thyroid peroxidase antibodies [TPOAb] as a marker) are critical exclusion criteria when selecting a cohort of patients, pregnant or not, for reference range determination purposes.

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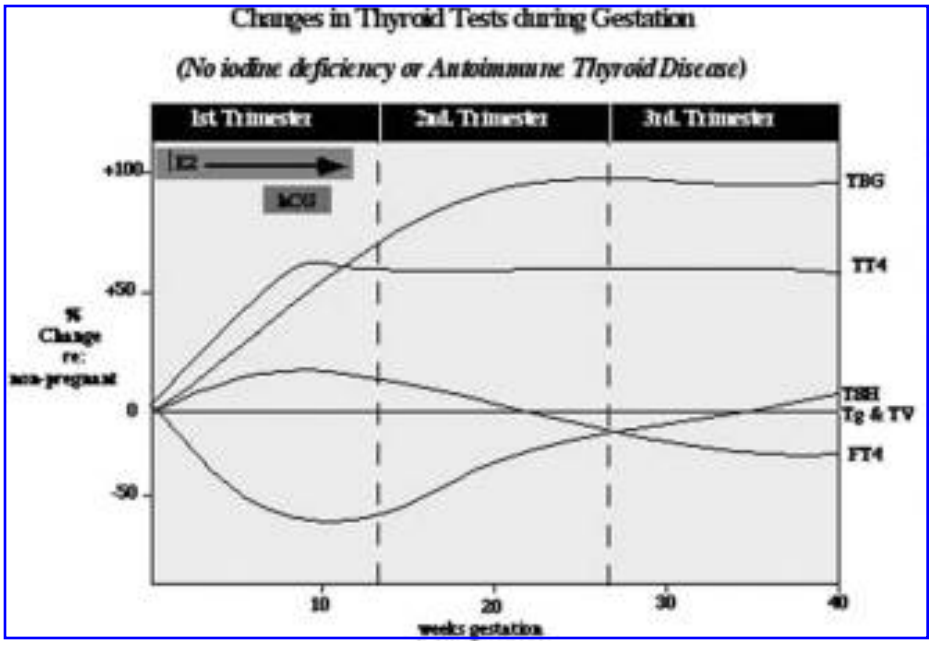

FIG. 1. Changes in thyroid test values during gestation in patients with no iodine deficiency and no autoimmune thyroid disease (AITD). In response, total thyroxine (TT_4) and free thyroxine (FT_4) concentrations rise sharply over the first trimester. As expected, the first trimester rise in FT4 is associated with a reciprocal and amplified suppression in thyrotropin (TSH). Thyroglobulin and thyroid volume assessed by ultrasound remain essentially unchanged.

- Much of the data have been generated in iodine-deficient populations and cannot be considered as normative data.
- There have been few large longitudinal studies that have included first trimester values.
- Few studies have rigorously excluded individuals with autoimmune thyroid disease, usually determined by the presence of TPOAb; inclusion of such individuals skews reference data.
- Current FT_4 methodology is problematic in that it is sensitive to the thyroxine-binding globulin (TBG) and/or albumin abnormalities characteristic of pregnancy in a method-specific and unpredictable manner.

Unfortunately, currently there are no reliable trimester-specific reference ranges for TSH. In addition to the problems listed above, the current available studies included early studies that use methods unable to detect the low TSH levels typical of the first trimester. The inclusion of patients with unusually high human chorionic gonadotropin (hCG), such as those pregnancies with severe hyperemesis (2,3) or with twin pregnancies (4), will skew the TSH lower reference limits. There is consensus, however, that the TSH reference range for first-trimester pregnancy should be lower than that for nonpregnant subjects (Fig. 2) (5). Until better data are available, the new recommended nonpregnant upper limit for TSH of 2.5 mIU/L (6) is an appropriate conservative upper TSH limit for first trimester pregnancy. Inasmuch as between-method biases for TSH are minimal, as future studies progress in pregnancy, there is no need for method-specific TSH ranges.

Our big challenge is to establish trimester-specific reference ranges for FT_4. Although we have generally considered equilibrium dialysis the most reliable method, equilibrium dialysis is too technically complex and expensive for routine use so that clinical laboratories typically use a commercial free thyroxine estimate test (FT_4E) test and not direct equilibrium dialysis. These FT_4E tests are all binding-protein sensitive to some extent in a method-specific manner (7). Currently, most FT_4 testing in clinical laboratories is based on two-step or labeled antibody methodology and do not measure free hormone directly. There are no appropriate trimester-specific, method-specific reference ranges for current FT_4E methods. Clearly no universal absolute FT_4 value can be established to define a low FT_4 across methods (Fig. 3) (8).

Perhaps we ought to reevaluate the clinical utility of our oldest thyroid test, total thyroxine (TT_4), in the setting of pregnancy. In contrast to FT_4, TT_4 methodology is more reliable. The TT_4 reference range for nonpregnant subjects has remained stable for more than two decades and is not method-dependent (9–15). These studies in populations with different iodine intakes and using different methodologies reveal remarkably comparable TT_4 values, both on an absolute and relative basis.

The TT_4 increase in pregnancy is predictable (1.5 times nonpregnant levels) and primarily relates to increased TBG. It is therefore appropriate at this time to use TT_4 in preference to FT_4 to evaluate pregnant patients provided that the nonpregnant reference limits are adjusted by a factor of 1.5 (16). A TT_4 cutoff of 100 nmol/L (7.8 μg/dL) may be appropriate for detecting a low FT_4 state in pregnancy (17). Unfortunately, TT_4 testing is increasingly becoming unavailable as laboratories replace TT_4 methods with FT_4E tests that are less reliable in the setting of pregnancy.

In considering establishing reference ranges for pregnancy, several problems need to be recognized: (1) current

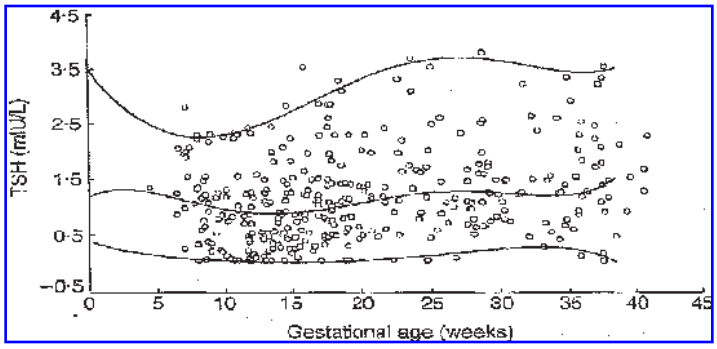

FIG. 2. Longitudinal study of thyrotropin (TSH) measurements in 343 pregnant patients from Hong Kong. Preexisting thyroid disease, hyperemesis gravidarum, trophoblastic disease, and preeclampsia were excluded. (Adapted from the Annals of Clinical Biochemistry [5]).

federal regulations, e.g., Institutional Review Boards (IRBs), Health Insurance Portability and Accountability Act (HIPAA), inhibit manufacturers from obtaining adequate clinically defined patient specimens for establishing reference ranges for pregnancy and other abnormal binding-protein conditions; (2) manufacturers are increasingly contracting outside the United States to acquire unusual specimens to overcome these regulatory restrictions; and (3) studies of non-U.S. populations with different iodine intakes, together with the use of insensitive methods for excluding autoimmune thyroid disease (AITD), may produce reference ranges that are inappropriate for the U.S. population. A satisfactory solution cannot rest with the local laboratory despite regulations requiring this, because it is increasingly difficult for laboratories to establish reference ranges independent of the manufacturer of the test.

In discussion:

Dr. P. Reed Larson: *Is there any basis for the difference between the two population TSH assays used (0.3 to 3.0 limit and 0.5 to 5.0)?*

Most labs are required to check the manufacturer's reference limits with their local population. That is very

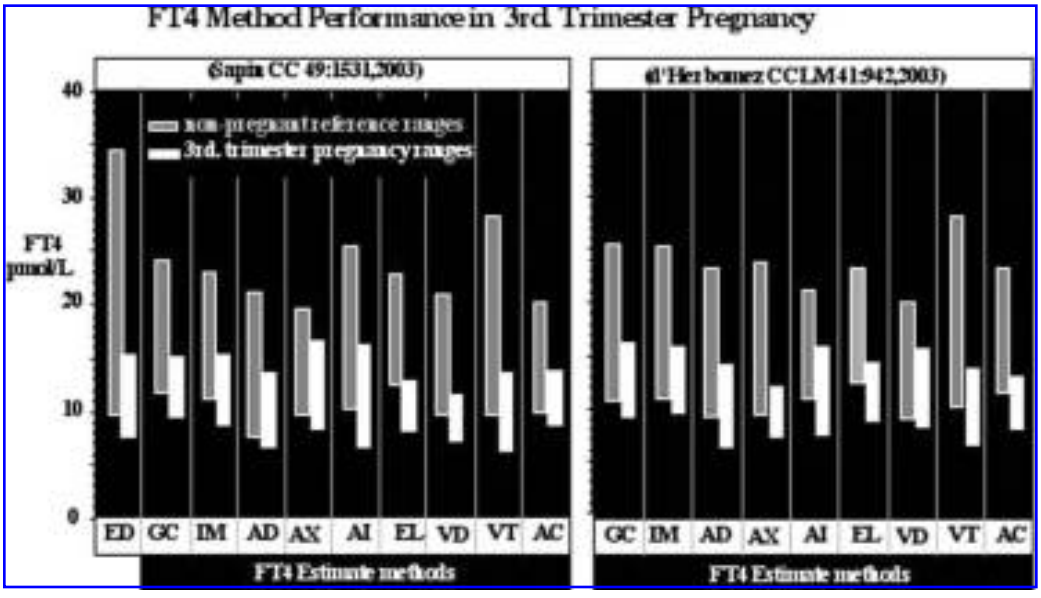

FIG. 3. Free thyroxine (FT_4) nonpregnant reference range values compared to third trimester pregnancy using different methods. ED, Direct Equilibrium Dialysis (Nichols, San Juan Capistrano, CA); GC, GammaCoat 2-step RIA (DiaSorin, Stillwater, MN); IM, Immulite (Diagnostic Products Corporation, Los Angeles, CA); AD, Advantage (Nichols); AX, AxSYM (Abbott Diagnostics, Abbott Park, IL); AI, AIA (Tosoh Bioscience, Tokyo, Japan); EL, Elecsys (Roche, Nutley, NJ); VD, VIDAS (bioMerieux, Durham, NC); VT, Vitros ECi (Ortho-Clinical Diagnostics, Raritan, NJ) and AC, ACS (Bayer Diagnostics, Tarrytown, NY). The only study involving equilibrium dialysis was the first study shown on the left, the other 9 methods were FT_4 estimate tests. Despite methodological improvements since 1991 absolute reference ranges for nonpregnant subjects still vary. Specimens from third trimester pregnancy patients gave some low values by all methods. In one method tested in both studies there was little overlap between the ranges for nonpregnant with pregnant subjects. Clearly no universal absolute FT_4 value can be established to define a low FT_4 across methods (6,7).

difficult to do, but how rigorously they exclude AITD and the quality of their antibody test determines the rigor of study population data. The lower limits are fairly comparable between TSH assays ranging between 0.2 and 0.4, but the upper limit is the problem.

Dr. John H. Lazarus: *Among pregnant population with normal iodine levels, what is the normal variation in protein binding in the first trimester?*

How FT_4 may be sensitive to TBG changes and albumin changes later in pregnancy, is unknown. Reference ranges based on third trimester data may not apply to the first trimester.

Dr. Glen F. Maberly: *The quality assurance component of CDC's worldwide lab network has standardized the whole approach to iodine estimates. More such population estimates are needed. CDC's NHANES website provides information on sample exchange and quality assurance.*
Dr. Robert C. Smallridge: *The difficulty of getting samples for establishing reference ranges may actually produce more carefully defined samples, if protocol and consent is required, and more reassurance that they do not have AITD, hyperemesis, etc. Carefully defined patient populations are important in understanding these new ranges.*

However, it is cheaper for the companies to go abroad, which is what they are doing.

Dr. Stephen LaFranchi: *What is the ideal screening test to use as early as possible in pregnancy (4–6 weeks)?*

TSH, since its suppression in the first trimester is reciprocal with the hCG, and in those with some degree of thyroid impairment, especially autoimmunity. TSH and TT_4 are probably the best combination of tests to evaluate the pregnant patient. The TSH upper range would probably be closer to 2.0, but 2.5 is a conservative limit for a first trimester pregnancy.

Dr. James E. Haddow: *Our first-trimester TSH data used a cutoff of 4 mIU/L, which we felt gave our study firm ground to know who will have a problem or not. A lower cutoff will dilute the population. If 2.0 is used, what percent of population do you lose?*

The Hong Kong study's TSH upper limit was 2.3 mIU/L for the first trimester, but did not exclude AITD. If 2.5 is considered the upper limit this would indicate those with TPOAb and abnormal TSH, and predict postpartum thyroiditis.

Dr. Haddow added: *that in future studies in order to capture a rich sample population, the percentile used should identify as "normal" as few individuals as possible to begin with, and then expand.*
Dr. Robert F. Vogt, NCEH/DLS Newborn Screening Branch: *The National Committee for Clinical Laboratory Standardization (NCCLS) is a long-standing clearinghouse for addressing such laboratory issues. It works through the manufacturers, government and academic sectors to develop consensus documents on the use of laboratory tests and other specifics. It may be useful to have them review the topics of thyroid tests and autoantibody tests in pregnancy.*

"Criteria for Diagnosis and Treatment of Hypothyroidism in Pregnancy"—Dr. Susan J. Mandel

Primary hypothyroidism during pregnancy can be detected by serum TSH measurement, but trimester-specific TSH normal ranges are needed because there are normal physiologic changes in serum TSH levels during gestation that may confound interpretation. In the absence of guidelines for universal screening for hypothyroidism, there are four groups of women at risk for thyroid deficiency during pregnancy.

1. Established hypothyroidism prior to pregnancy. Prior to conception, a woman may already be receiving T_4 therapy for diagnosed hypothyroidism. Using the data from NHANES III, T_4 therapy should be optimized prior to conception by titrating the dose to a serum TSH level less than 2.5mIU/L. There are now nine studies that have shown that the majority of hypothyroid women require an increase in thyroxine dose during pregnancy (Table 1) (18–26). The majority of women will require a dosage increase in the first trimester as determined by a serum TSH level above the normal range for that assay rather than by pregnancy-specific TSH ranges. The median time of dosage increase is 8 weeks' gestation (19). The required T_4 dosage increment to normalize the serum TSH level may depend upon both the degree of the initial serum TSH elevation (Fig. 4) (22) and the etiology of the maternal hypothyroidism (22). Of studies that delineated the hypothyroid women, 35%–45% with AITD required a dosage increase, as opposed to 70%–75% of athyreotic women (e.g., from ^{131}I ablation or thyroidectomy) (Fig. 5) (22). If trimester-specific TSH normal ranges were used, the dosage of even more hypothyroid women would probably increase. The median thyroxin increment of the nine studies was approximately 39 μg/d with athyreotic women requiring a larger increase (mean, 52 μg/d) than those with lymphocytic thyroiditis (mean, 28 μg/d) (19). The thyroxine dosage should be titrated to gestation spe-

TABLE 1. PREGNANT WOMEN REQUIRING LEVOTHYROXINE DOSAGE INCREMENTS IN PREGNANCY

		Pregnancies		
Author		*Total number*	*Elevated TSH number*	*(%)*
Pekonen	(1984)	37	8	(27)
Mandel	(1990)	12	9	(75)
Tamaki	(1990)	6	3	(50)
Kaplan	(1992)	42	27	(64)
Girling	(1992)	33	7	(21)
McDougal	(1995)	20	20	(100)
Caixas	(1999)	41	19	(46)
Abalovich	(2002)	95	66	(70)
Chopra	(2003)	13	6	(46)
Overall		299	165	(55)

TSH, thyrotropin.

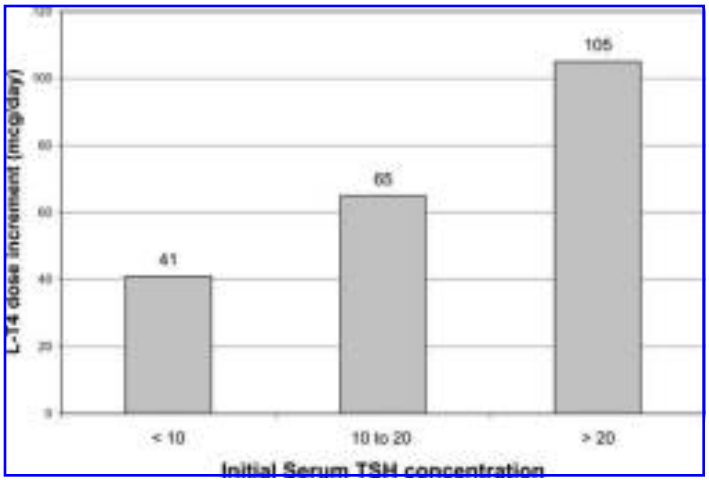

FIG. 4. Mean L-T_4 dosage increment to achieve euthyroidism in pregnant hypothyroid women is related to the initial pregnancy concentration of serum TSH. (22)

cific TSH normal values, rather than to those used for the nonpregnant population.

2. Autoimmune thyroid disease prior to pregnancy. Between 5% and 10% of women of reproductive age may have positive antithyroid antibodies with serum TSH levels in the normal assay range (22–24). When followed prospectively through gestation, despite the expected reduction in antibody levels in the third trimester, 30% of such women had a serum TSH level greater than 3 mIU/L, with 16% of values above 4 mIU/L (23). If a woman is known to have AITD prior to conception, a serum TSH level should be obtained. In addition, women with type 1 diabetes (25) and other autoimmune disorders (rheumatoid arthritis, Sjögren's disease, etc.), or a family history of AITD are at increased risk for AITD themselves and should have a serum TSH level measured prior to conception, or if not done at that time, during pregnancy.
3. Serum TSH level in the upper normal range prior to pregnancy. There are no data to predict the gestational thyroid function of a nonpregnant woman with a serum TSH between 2.5–5 mIU/L (above the 96th percentile of the NHANES III reference population [24]). The options would be either to initiate a low dose of T_4 titrated to a serum TSH less than 2.5 mIU/L or to monitor TSH levels during gestation and initiate T_4 therapy only if the serum TSH rises above trimester-specific normal ranges.
4. Elevated TSH detected for first time during pregnancy. During pregnancy, the prevalence of serum TSH levels above normal assay reference ranges (not pregnancy reference ranges) is 1%–2% (22,31). In the vast majority of such women, subsequent measurement of thyroid hormone levels falls in the normal assay range, with only a small fraction having overt hypothyroidism. The optimal therapy for these women is titration of T_4 therapy to trimester-specific normal TSH ranges. On average, the increased T_4 requirement during pregnancy is approximately 2 μ/kg per day for replacement dosing, rather than 1.6 μg/kg per day used for the nonpregnant patient.

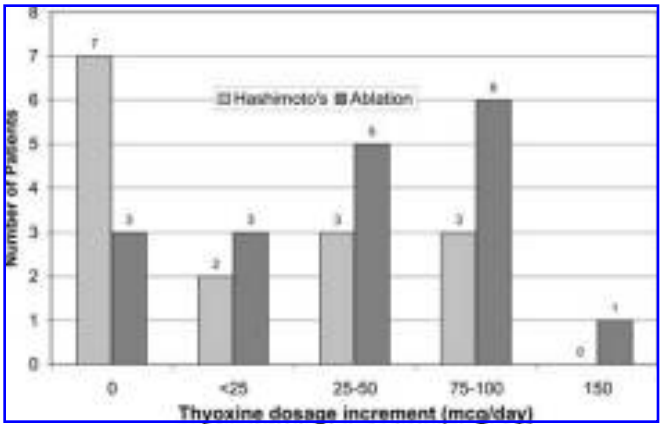

FIG. 5. L-T_4 dosage increments to achieve euthyroidism in pregnant hypothyroid women are greater if the gland has been ablated than if the patient has AITD (22).

Treatment recommendations were:

- Initiate LT_4 therapy if serum TSH greater than 2.5 mIU/L (confirmed) prior to pregnancy.
- Titrate LT_4 to serum TSH at less than 2.5 mIU/L prior to pregnancy for women with established hypothyroidism and women who have just begun LT_4 therapy.
- Check serum TSH level in early pregnancy.
- Base LT_4 dosage adjustments during pregnancy upon trimester-specific TSH normal ranges.
- The magnitude of LT_4 dosage increment may depend upon etiology of hypothyroidism.
- TSH should be monitored every 6–8 weeks during pregnancy, sooner (4–6 weeks) if LT_4 dosage adjustment is made.
- Separate LT_4 ingestion by at least 4 hours from iron supplements and iron-containing multivitamins, calcium supplements, and soy milk.
- If elevated serum TSH is first detected during pregnancy, initiate LT_4 at 2.0 μg/kg per day.

In discussion:

Dr. Glen F. Maberly: *In your risk factors, you didn't mention iodine nutrition. If you look at the levels where TSH are elevated in higher a proportion, for instance in Italy, but less in Japan, you could almost correlate iodine nutrition of those countries with different ranges of what you might expect in TSH because of iodine deficiency. So I wonder whether the population here has adequate iodine nutrition.*

That is a critically important point. I was restricting myself to hypothyroidism in the absence of iodine deficiency—so I didn't include iodine deficiency or borderline iodine deficiency as a risk factor. But I do think that's a critical point that I think was made yesterday. Perhaps one of the things that will come out of this meeting is an emphasis on ensuring iodine health worldwide for women in their reproductive years.

Dr. John H. Lazarus: *Should the risk factor of an iodine deficient area be better accounted for, especially before using T_4?*

Yes, that is a critical point. This presentation addressed hypothyroidism in the absence of iodine deficiency, but perhaps iodine should be supplemented for reproductive-age women worldwide.

Dr. Robert C. Smallridge: *Is there any danger to overtreating? What is known about suppressed TSH in very mild FT_4 elevations during pregnancy and subtle changes at the other end of the TSH spectrum?*

As Dr. Vulsma mentioned yesterday, there is the rare risk of central congenital hypothyroidism that resulted from Graves' disease during pregnancy, but this has not been found in someone who is exogenously treated, so that particular risk to the baby is not an issue. In terms of complication to the mother, it is plausible that miscarriage rates may rise somewhat. It is possible that mild over treatment can do harm. But "over treatment" needs definition based on normal pregnancy ranges, and the ability to diagnose over treatment may be limited by methodological issues.

Dr. Smallridge advised caution to avoid unintended effects. *The Colorado study indicated that of nonpregnant individuals on thyroid hormone, 40% were on an incorrect dose, and half of those had suppressed TSHs.*

It is unlikely that someone pregnant would be overtreated if appropriate TSH testing guidelines are followed.

Dr. Gabriella Morreale de Escobar: *If the feedback mechanisms for nonpregnancy do not work similarly for pregnancy (e.g., due to hCG, estrogen), why are the treatment schedules based on TSH values? Sufficient T_4 should be given to have a normal FT_4 value as the end point. TSH might be totally misleading. Shouldn't you be measuring T_4? There has been no mention in the whole presentation what T_4 levels you achieve with the any of the treatment regimens.*

Dr. Reed Larsen: *We found no difference in the net TSH/FT_4 ratios in hypothyroid women during treatment in pregnancy; both were normal. However, while the median TSH increase in his study occurred at approximately 8 weeks, it was earlier in the assisted reproductive patients. Those patients probably should begin increased T_4 within a few weeks of conception. Overtreatment is unlikely, since 30% of the indigenous T_4 output would probably be suppressed, rather than TSH. But T_4 takes 5 weeks to equilibrate to a change in dose, so increasing at 8 weeks will normalize FT_4 by approximately 13 weeks gestation.*

Dr. Daniel Glinoer: *Another consideration to increasing dosage during pregnancy is the interference in the absorption of T_4 when taken with other than drugs or substances (e.g., calcium, iron, etc.). The uptake of thyroid hormones may be variable in some women due to digestive trouble.*

From presentations yesterday, we know that subclinical hypothyroidism could have a 2%–3% prevalence in an unselected pregnant population. Whether national screenings are sensible for that percentage bears discussion.

Dr. Reed Larsen emphasized the importance of the increased thyroid hormone requirements during normal pregnancy and suggested strategies in managing patients with known hypothyroidism planning conception or becoming pregnant.

In pre-pregnancy counseling, the physician should provide written explanations to the patient about the importance of thyroid hormone for fetal development and inform them that their LT_4 requirement will likely increase during gestation. The LT_4 dosage should be optimized by ensuring that the serum TSH is in the low–normal range prior to conception in patients with primary hypothyroidism. In the rare patients with central hypothyroidism, the FT_4 index should be in the upper half of the normal range.

Written instructions should be given to patients and a laboratory requisition provided to allow them to obtain a serum TSH as soon as pregnancy is confirmed and to notify their primary care physician, endocrinologist, and/or obstetrician for advice regarding their levothyroxine dosage. Either with their physician's advice (or perhaps even without it) the dosage of LT_4 should be increased by approximately 30% (two daily doses per week) when pregnancy is confirmed. The TSH should be monitored every 4 weeks thereafter during the first trimester, with appropriate increases as necessary, remembering that a typical athyreotic patient requires a 40% increase in their dosage. The levothyroxine replacement dose can be returned to its pre-pregnancy level at the time of delivery.

While the issue of whether or not all women planning conception should have a screening TSH to test for primary hypothyroidism has generated considerable discussion pro and con, my personal opinion is that there should be a low threshold for performing TSH testing in this group. Patients with a family or personal history of thyroid disease, goiter, diabetes, history of spontaneous abortion, or any symptoms suggesting hypothyroidism, should have this test. With these steps, as well as careful monitoring of TSH, we should be able to maintain normal thyroid hormone availability to the fetus during this critical period of development before fetal thyroid maturation occurs.

Discussant: Dr. Rosalind S. Brown presented information on the cognitive outcome in children after tsh receptor blocking antibody-induced congenital hypothyroidism: a model of fetal and maternal hypothyroidism. She pointed out that TSH receptor blocking antibodies (Abs), present in the pregnant mother, being IgGs, can be transmitted transplacentally to the fetus and, if sufficiently potent, can be a cause of both fetal and maternal hypothyroidism. Because, by analogy with rodent data, the TSH receptor is not expressed until ap-

proximately 13 weeks' gestation and not upregulated until the serum TSH begins to rise in the second half of pregnancy (33,34), fetal hypothyroidism in this model is dependent upon maternal hypothyroidism alone in the first half of pregnancy, and combined fetal and maternal hypothyroidism in the second half. Studies in Japan have reported severe cognitive delay (mean IQ 67, range 54–76) in 5 of 23 babies with TSH receptor blocking Ab-induced congenital hypothyroidism (CH) despite early and adequate postnatal therapy. In contrast, we observed no difference in verbal, performance, or full-scale IQ in 6 babies with transient CH caused by TSH receptor blocking Abs compared to their sibling controls (full-scale IQ 108 ± 21 versus 104 ± 17.7). In three of these mothers, this occurred despite severe hypothyroidism in the first trimester (mean T_4 1.1 μg/dL, mean TSH 44 mU/L) that required as much as 0.3 mg to 0.45 mg LT_4 to normalize. In contrast to the Japanese mothers all of whom had severe hypothyroidism in the third trimester of pregnancy, the serum T4 or FT_4 in all the mothers we studied was normal, and the TSH was either normal or mildly elevated in the third trimester.

In summary:

1. TSH receptor blocking Ab-induced CH, a model of combined maternal and fetal hypothyroidism during gestation, is associated with more severe cognitive delay than either fetal or maternal hypothyroidism alone, probably because maternal T_4 is unavailable to compensate for the fetal hypothyroidism
2. This disorder should be suspected if unusually high doses of LT_4 are required to normalize maternal thyroid function during gestation,
3. In contrast to the Japanese data (34) with the author's data (35), it appears that adequate maternal T_4 replacement in the latter half of pregnancy may be protective for fetal neurologic development even if blocking antibodies are present.

She hypothesized that:

- The most critical time for thyroid hormone-dependent brain development may be the third trimester and not earlier during pregnancy.
- Because the third trimester is important for cerebellar development as well as myelination, inadequate treatment of mothers with TSH receptor blocking Abs during pregnancy may result in more severe neurologic impairment of their babies than is seen in other causes of CH.

The conclusion was that it is critical to know the etiology of maternal hypothyroidism in order to evaluate the critical time for fetal cognitive development. If only maternal hypothyroidism is present, the first half of pregnancy is critical. But if both maternal hypothyroidism and fetal hypothyroidism are present, as with blocking antibodies or iodine deficiency, the data are consistent that the third trimester seems to be the critical period. This has important implications to the optimal timing of maternal thyroid screening.

The discussion included that a number of the women were diagnosed and treated in the first trimester, but it took time to normalize their levels, and some remained hypothyroid despite treatment.

Dr. Joanne Rovet noted that using only the full IQ score does not include other abilities related to thyroid hormone, such as attention and memory and executive processing. There may still be deficits in the children exposed in the first two trimesters that would not be measured by the presented variables.

Discussant: Dr. G. Robert DeLong presented data on timing of iodine repletion of pregnant women in southern China from Studies in Xinjian Uyghur Autonomous Province, China. His studies pointed out a need for iodine during gestation for fetal development and also a role for thyroid hormone and iodine in system generation.

Studies were done in Hotien County of Xinjiang province in China (36). This is an area of severe iodine deficiency populated by a central Asian, Turkik people. At the time of study, the conventional wisdom was that iodine was essential in the first trimester for brain formation. But the birth abnormalities of the first trimester did not parallel the conditions seen in iodine deficiency. The cohort consisted of children from age 3 years down to newborns. They were treated as soon as they were examined, as were pregnant women in all trimesters. Three measures of outcome were used: neurologic examination (a subtle, hard-to-quantify instrument), DQ and IQ (age 2 and later age 6 years), and head circumference (very quantifiable).

The time of treatment with iodine correlated well with head circumference. The incidence of microcephaly (defined as anything > 2 standard deviations from the American norm) was 20%. Treating the mothers in the third trimester showed little difference to those not treated or treated just after birth, but the infants did improve after approximately a year. Those treated in the second trimester had significantly fewer neurologic abnormalities than those not treated. However, the head circumference did not improve for those treated in the first trimester, and the outcomes of those who were treated in the early part of the first trimester paralleled those who were untreated.

Head circumference has a virtually straight-line relationship to brain weight in young children, and so serves as a good index of brain growth. Measures of head circumference versus time of iodination were charted. Those untreated at age 2 had a small head, but head circumference increased among those treated earlier. A 20-point IQ/DQ difference was also charted between those treated in the second trimester versus those untreated. More extensive testing at age 5 years showed the same pattern, although more exaggerated for improvement of those treated in the second trimester and worse for those untreated.

Summary: It was concluded that the end of the second trimester appears to be a critical time for iodine, and thus for thyroid hormone, to be present to prevent permanent brain impairment. This corresponds with data from laboratory animals, and most intriguingly with experience in supplementing premature infants with thyroid hormone, which demonstrated a significant 18-point improvement in DQ at age 2 years if supplementation occurred before 27 weeks' gestational age.

An interesting and potentially related finding was drawn from a study of treating premature infants with thyroid hormone. If done after 27 weeks of pregnancy (third trimester), there was no benefit; there might even have been a slight decrease in DQ at 2 years. If treated before 27 weeks, the out-

come was a positive improvement in DQ of 18 points by age 2.

Another intervention, treating the entire population with adequate iodine by adding it to drip irrigation water, succeeded in reducing infant mortality rates, particularly neonatal rates, by 50% (37). He speculated that thyroid hormone and iodine are essential to develop the systems that are critical in preventing infant mortality through abnormalities in the immunological, cardiovascular, and other systems. There is very little information in the literature on this.

Discussion included: A participant asked: *Why were early treatments in your study as bad as none at all?*

The theory is that the iodized oil dissipates after an initial boost.

Dr. Glinoer: *It is also surprising that, regardless of when treated, there is no benefit except in the second trimester. And the head circumferences, regardless of time of treatment, were all 1–2 standard deviations value below zero. Did none of them have a normal head circumference?*

That is correct. The study examined the children of officials of the same ethnicity, but with a better standard of living, who eat well and get plenty of iodine. They matched the American norms.

Dr. Morreale: *In the later studies, where iodine was added to the water, do the data of children in the first trimester, when the iodine addition began, show a worse outcome than those in the second trimester?*

There are no such data. The addition was a gradual process, inserting iodine into the crops and food over 2–3 years.

Dr. Maberly: *Treatment with oil capsules tends to deliver very high initial iodine levels that rapidly drop off, and there is great variability between individuals as shown by excretion patterns in populations taking iodine orally. Perhaps there was a blocking effect of iodine followed by a beneficial effect, and then a deficiency. That would make interpretation of the treatment difficult, since physiologic doses were not being delivered in a constant fashion.*

Were these findings only relevant to severely iodine-deficient populations?

Yes.

Dr. Dunn: *Are there any data known of patients who might have gotten an excessive iodine dose (e.g., from radiography) in the first trimester?*

Dr. Vulsma reported a pregnant Dutch woman who was euthyroid, but who received iodized oil in Africa. The child, delivered months later, was severely hypothyroid with very high iodine content, but otherwise appeared to be a normal, healthy child. He was treated with T_4.

Summary: Are Detection and Treatment of Thyroid Insufficiency in Pregnancy Feasible?

What we know:

1. For TSH there is good agreement between methods in terms of absolute values, that is, there is no need for method-specific TSH reference ranges.
2. TSH can be used as marker for hypothyroidism in pregnancy, except when there is severe iodine deficiency usually evidenced by elevated serum thyroglobulin.
3. The nonpregnant TSH upper limit of 2.5 mIU/L can be used as a conservative guide for pregnancy, but a 2.5 limit is likely to be too high for first trimester pregnancy. We need more longitudinal studies of iodine sufficient populations without evidence of autoimmune thyroid disease.
4. Current FT_4E methods are sensitive to abnormal binding-protein states such as pregnancy. (*Need method-specific, trimester-specific and possibly population-specific FT_4 reference ranges.)*
5. There is no absolute FT_4 value that will define hypothyroxinemia across methods.
6. TT_4 changes in pregnancy are predictable and not method-specific.
7. Laboratories should retain TT_4 testing for assessing the thyroid status of pregnant patients.
8. The TT_4 reference range for pregnancy can be calculated by multiplying the nonpregnant reference limits of the method by 1.5.
9. TT_4 correlates with hCG and inversely with TSH in the first trimester.
10. A TT_4 below 100 nmol/L (7.8 μg/dL) is a reasonable indicator of hypothyroxinemia in pregnancy.
11. Women with known hypothyroidism and receiving LT_4 before pregnancy should plan to increase their dosage by 30 to 60% early in pregnancy.
12. Women with AITD, and elevated TSH prior to pregnancy are at increased risk for thyroid insufficiency during pregnancy and postpartum thyroiditis and should be monitored with TSH and TT_4 during pregnancy.
13. When TSH is found to be elevated in pregnancy, test should be repeated, and if persistently high, thyroxine treatment should be started at approximately 2 μg of thyroxine per kilogram per day, titrating TSH levels to trimester specific TSH ranges.
14. The practice of test-kit manufacturers of using non-U.S. populations with different iodine intakes to establish reference ranges for pregnancy should be discouraged.
15. Reference ranges constructed without consideration of iodine or thyroid autoimmunity status are worthless.

What we do not know:

1. Trimester-specific reference ranges for TSH, especially in the first trimester;
2. Method- and trimester-specific reference ranges for FT_4 estimate methods;
3. The specific effects of overtreatment with LT_4 on mother and fetus; and
4. The extent to which U.S. iodine nutrition influences thyroid analytes during pregnancy.

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